CASE REPORTS

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Hyperhistaminemia and Peptic Ulcer

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INCREASED CIRCULATING HISTAMINE LEVELS have been found in a number of disease states including bronchial asthma, some allergic conditions, cutaneous burns and eosinophilia from various causes. Using Code's modification[1] of the method of Barsoun and Gaddum, normal values have been established at between 1.08 and 8.5 μg, expressed as free histamine base per dl whole blood. In the above diseases, elevated values are seldom more than 20 μg per dl. In the myeloproliferative diseases there are numerous reports of unusually high levels—that is, more than 100 μg per dl and as high as 2,000 μg per dl. Reports appeared in the American literature in 1937,[1] in the French literature in 1937[2] and in the German literature in 1941.[3] Since then results of numerous studies have confirmed these observation;[4-13] however, symptoms and signs resulting from the pharmacologic effects of hyperhistaminemia rarely have been recognized.

Gilbert, Warner and Wasserman[14] in 1966 were the first to report cutaneous and gastrointestinal symptoms associated with polycythemia vera and hyperhistaminemia. They noted a rough correlation between the number of basophils, histamine level, and the presence of pruritus, urticaria and gastrointestinal symptoms. They also reported relief of pruritus and urticaria with the antihistamine, cyproheptadine hydrochloride, despite a lack of change in histamine levels in the blood. There was no mention of the effect, if any, on gastrointestinal symptoms. Their studies indicated that there was little relief with the use of other medications including diphenhydramine hydrochloride, tripelennamine hydrochloride, chlorpheniramine, trimeprazine tartrate, chlordiazepoxide hydrochloride, meprobamate and prednisone. Moreover, the authors pointed out that pharmacologic effects of hyperhistaminemia were not uncommon in polycythemia vera, but seldom seen in chronic myelogenous leukemia, and they felt that this might be due to differences in binding of the histamine within the cell or in the rate of release of the histamine from the cell.

The first report of histamine symptoms in chronic granulocytic leukemia similar to those seen in systemic mast cell disease was reported in 1973 by Youman and co-workers[15] from the Mayo Clinic. The patient in their report had chronic granulocytic leukemia with basophilia (basophil count as high as 91,250 per cu mm), intense and disabling pruritus, cold urticaria and epigastric discomfort. Total blood histamine levels in this patient exceeded previously reported levels, reaching as high as 5,000 μg per dl on one occasion. Gastric analysis showed concentrations comparable to maximum histamine stimulation testing. However, upper gastrointestinal x-ray studies did not document peptic ulceration despite the high histamine levels. Pruritus and urticaria partially responded to treatment with diphenhydramine hydrochloride and brompheniramine maleate.

The first report of documented peptic ulceration associated with hyperhistaminemia and chronic granulocytic leukemia appeared in 1976.[16] In a patient admitted to the National Institutes of Health, gastric secretory levels strongly suggestive of the Zollinger-Ellison syndrome with normal serum gastrin levels were found.[16] A large actively bleeding postbulbar ulcer and two smaller duodenal ulcers, as well as a benign gastric ulcer, were seen on endoscopy. The patient's condition was unresponsive to the usual therapy for ulcer management but symptoms improved following oral administration of metiamide, 400 mg every four hours. The acid secretory rate fell from 6.5 mEq per 15 minutes to levels compatible with persistent achlorhydria for a period of 2½ hours following administration of metiamide. Unfortunately the patient died of leukemia within a few

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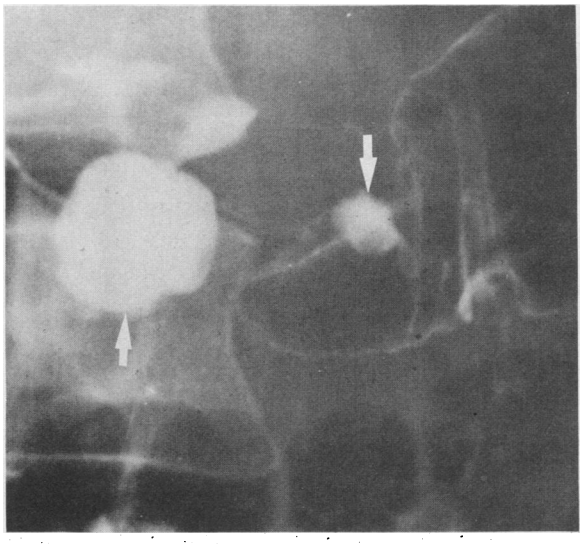

Figure 1.—X-ray film of the upper gastrointestinal region showing two ulcers (arrows).

weeks after treatment was started. At autopsy a healed ulcer, 0.3 cm by 1.0 cm, in the second portion of the duodenum was noted.

The following is the first documented case of chronic myelogenous leukemia with hyperhistaminemia, maximum gastric secretory activity, and multiple gastroduodenal ulceration responsive to administration of the histamine H_2 receptor blocking agent cimetidine.

Report of a Case

Acute promyelocytic leukemia was diagnosed in a 40-year-old man in July 1976. Chemotherapy was carried out and there was remission of all symptoms. In January 1977 findings on bone marrow studies were felt to be within normal limits; however, in March 1977 another bone marrow study showed a relapse with 40 percent blasts. In April 1977 bone marrow cytogenetics showed the Philadelphia chromosome and the diagnosis was changed to chronic myelogenous leukemia. On June 9, 1977, the patient was seen in the outpatient department, with complaint of itching and a skin rash. The following day he noted abdominal pain in the epigastric region accompanied by anorexia. Because of an apparent relapse of leukemia and the onset of abdominal pain, the patient was admitted to hospital on June 12, 1977.

On physical examination at the time of admission the following findings were noted: erythematous crusting lesions with multiple excoriations; blanching urticarial lesions; the liver was enlarged 5 cm below the right costal margin but the spleen was not definitely palpable. All blood studies and urine analyses gave findings within normal limits, other than a leukocyte count of 48,200 per cu mm with 50 percent basophils and elevated levels of alkaline phosphatase (93 units per liter) and lactic dehydrogenase (484 units per liter). Because of persistent and increasing abdominal pain, an upper gastrointestinal x-ray study was done (Figure 1). Two ulcers were easily seen, one in the superior portion of the antrum (1 cm in diameter) and another in the duodenal bulb (3 cm in diameter). Gastric analysis with maximum betazole hydrochloride (Histalog) stimulation showed a pronounced hypersecretory state (Table 1).

The patient was placed on a regimen of antacids consisting of magaldrate (Riopan), 60 ml per hour. Treatment with hydroxyurea was started for the relapse of leukemia. The patient noted no relief of abdominal pain and, while treatment was under way, massive upper gastrointestinal hemorrhage developed. Multiple blood transfusions were necessary to maintain the hematocrit at acceptable levels. Upper gastrointestinal endoscopy at this time showed a 1 cm benign appearing antral ulcer surrounded by edema and hyperemia. In addition, a large ulcer in the duodenal bulb covered by fresh blood clot was seen. Several hours after endoscopy, massive blood loss occurred again and the patient was taken to the operating room where hemigastrectomy and Bill-

TABLE 1.—*Results of Gastric Analysis With Maximum Betazole Stimulation*

	Basal		*After betazole**				
Time (minutes) ..	0-30	30-60	0-15	15-30	30-45	45-60	60-75
Volume	206.00	178.00	116.00	88.00	162.00	162.00	131.00
pH	2.20	2.10	2.20	2.50	2.10	2.20	2.60
Acid mEq/L	112.80	126.60	110.40	87.60	109.80	89.90	85.00
Acid output	23.24	22.53	12.81	7.71	17.79	14.55	11.56

BAO (basal acid output) = 45.77 mEq per hour
MAO (maximal acid output) = 56.71 mEq per hour
PAO (peak acid output) = 64.68 mEq per hour
BAO/MAO = 0.81

*1.5 mg per kg of body weight

TABLE 2.—*Gastric Analysis Two Weeks After Operation but Before Cimetidine Administration*

Time (minutes) ..	0-30	30-60
Volume	116.0	84.0
pH	2.2	2.2
Acid mEq/L	66.0	56.0
Acid output	7.6	4.7

BAO (basal acid output) = 12.3 mEq per hour

TABLE 3.—*Gastric Analysis After Two Weeks of Cimetidine Administration**

	Basal	*After betazole*†	
Time (minutes) ..	0-30	0-30	30-60
Volume	4.0	74.0	44.00
pH	7.6	5.4	3.30
Acid mEq/L	0.0	13.6	26.20
Acid output	0.0	1.0	1.15

BAO (basal acid output) = 0

*300 mg
†1.5 mg per kg of body weight

roth II anastomosis were done. Vagotomy was not technically possible because of massive hepatomegaly. Gastrin levels preoperatively at the time of gastric analysis were reported as 77 pg per ml (N = less than 100). Whole blood histamine level was reported as 2,376 μg per dl (N = 4 to 7). Despite the hemigastrectomy, gastric analysis two weeks after the operation showed a basal acid output of 12.3 mEq per hour with acid concentrations of 66 mEq per liter at between 0 and 30 minutes and 56 mEq per liter at between 30 and 60 minutes (Table 2). At the time of this study the leukocyte count was 76,400 per cu mm with 88 percent basophils. In view of this, administration of cimetidine, 300 mg four times per day, was started and the patient received 100 rads of total body irradiation to diminish the leukocyte count.

After two weeks of cimetidine therapy and when the leukocyte count was 52,100 per cu mm with 89 percent basophils, gastric analysis was repeated and a pronounced decrease in basal secretory rate was found (Table 3). Blast crisis was now treated successfully with cytosine arabinoside and 6-thioguanine and during the next three months the patient was without abdominal symptoms. On August 24, 1977, the leukocyte count was 8,500 per cu mm with 4 percent basophils and the total blood histamine level was 17 μg per dl. Administration of cimetidine was discontinued. In October 1977 the patient returned to the clinic complaining of midepigastric pain of several days' duration and one episode of coffee-ground emesis. The leukocyte count was 58,600 per cu mm with 68 percent basophils and the total blood histamine level was 6,591 μg per dl. Blast crisis was confirmed by bone marrow examination but treatment was initially withheld because of a concurrent cellulitis. Cimetidine therapy was started. The abdominal pain disappeared and there were no further episodes of gastrointestinal hemorrhage. The blast crisis was again successfully treated.

The abdominal pain remained in abeyance with cimetidine therapy until January 1978. The patient then presented to the outpatient clinic with midepigastric pain that had begun after his supply of cimetidine had run out. The pain again was easily controlled by administration of cimetidine and antacids but once more the leukocyte count (71,100 per cu mm with 53 percent basophils) was elevated and examination of bone marrow indicated blast crisis. Chemotherapy induced pronounced pancytopenia; pneumonia and Escherichia coli and Klebsiella sepsis developed, and the patient died. Postmortem examination was not permitted.

Discussion

This is the second reported case of hyperhistaminemia associated with chronic myelogenous leukemia resulting in severe gastrointestinal ulceration. Gastric secretory rate and basal acid output/maximal acid output ratios were similar to those seen in the Zollinger-Ellison syndrome. However, the stimulus to secretion was histamine rather than gastrin. Control of the gastric response to hyperhistaminemia was satisfactory with the use of the H_2 blocking agent cimetidine. With remission of leukemia and a decrease in basophilia, the histamine level decreased almost to normal. Hyperhistaminemia recurred with relapse, but gastrointestinal symptoms were controlled during cimetidine treatment.

Pharmacologic effects of hyperhistaminemia in patients with systemic mastocytosis have been reported frequently. Because the basophil is the only circulating myelocyte with a histamine content similar to that of tissue mast cells, it is difficult to explain why the syndrome of *hyperhistaminemia* has not been reported more frequently in association with the myeloproliferative diseases, particularly when significant basophilia exists. Conceivably, symptoms of pruritus, the presence of urticaria and varied gastrointestinal symptoms may be ascribed to the underlying myeloproliferative disease rather than to hyperhistaminemia. On the other hand, histamine effects may be rare

because histamine is tightly bound within the cell boundaries of the circulating basophils. Further studies of total blood histamine as well as plasma histamine levels and their correlation with gastric secretory rates in patients with myeloproliferative disease are needed. Determining levels of histamine, evaluating gastric secretory status and obtaining x-ray films of the upper gastrointestinal region in patients with myeloproliferative diseases should be given higher priority.

Summary

The mast cell (tissue) and basophil (circulating) are known to have high concentrations of histamine. Proliferation of mast cells (systemic mastocytosis) often results in hyperhistaminemia with resultant pharmacologic effects (pruritus, urticaria and the like). Similarly, proliferation of basophils (myeloproliferative diseases) is associated with hyperhistaminemia. It is odd that reports of pharmacologic effects of histamine on target organs (skin, lungs, heart and stomach) have been reported in rare instances only. This case of chronic myelogenous leukemia is the second that has been reported involving histamine stimulation of gastric acid secretion and peptic ulceration of a magnitude similar to the acid secretion resulting from hypergastrinemia. It is the first case showing adequate control of the hyperacid secretory state by cimetidine treatment. It is possible that pharmacologic effects of hyperhistaminemia in the myeloproliferative diseases is more common than the literature indicates.

REFERENCES

1. Code CF, MacDonald AD: The histamine like activity of blood. Lancet 2:730-733, 1937
2. Marcou I, Gingold N, Parhon CC Jr: L'histamine dans les maladies du sang. Bull Acad do méd de Roumaine 2:366-371, 1937
3. Went F, Rex-Kiss B: Ueber den Histaminhalt des Blutes bei Pathologischen Anderungen des Blutbildes und Blutdruckes. Z klin Med 139:157-162, 1941
4. Shimkin MB, Zon L, Crigler CW: Blood histamine in gastric cancer and peptic ulcer. Proc Soc Exp Biol and Med 52:335-338, 1943
5. Shimkin MB, Saperstein L, Goetzl FR, et al: Blood histamine in leukemia and erythremia. J Nat Cancer Inst 9:379-387, 1948
6. Thiersch JB: Histamine and histaminase in chronic myeloid leukemia of man—I. Histamine in the blood of chronic myeloid leukemia; II. Histamine and histaminase in the blood of myeloid leukemia under and after deep X-ray treatment. Aust J Biol and Med Sc 25:73-74, 75-77, 1947
7. Valentine WN, Lawrence JS: Studies on blood histamine partition of blood histamine before and after clotting in health and disease states. Am J Med Sc 216:619-624, 1948
8. Valentine WN, Pearce ML, Lawrence JS: Studies on the histamine content of blood with special reference to leukemia, leukemoid reactions and leukocytosis. Blood 5:623-647, 1950
9. Shimkin MB, Beirman HR, Low-Beer BVA, et al: Blood histamine in myelogenous leukemia. Cancer 4:570-578, 1951
10. Valentine WN, Beck WS, Follette JH, et al: Biochemical studies in chronic myelogenous leukemia, polycythemia vera and other idiopathic myeloproliferative disorders. Blood 7:959, 1952
11. Brandt L, Cederquist E, Rorsman H, et al: Blood histamine and basophil leukocytes in polycythemia. Acta Med Scan 176: 745-750, 1964
12. Horakova Z, Keiser HR, Beaven MA: Blood and urinary histamine levels in normal and pathological states as measured by a radiochemical method. Clin Chem Acta 79:447-456, 1977
13. McCarthy DM: Report on the United States experience with cimetidine in Zollinger-Ellison syndrome and other hypersecretory states. Gastroenterology 74:453-458, 1978
14. Gilbert HS, Warner RRP, Wasserman LR: A study of histamine in myeloproliferative disease. Blood 28:795-806, 1966
15. Youman JD, Taddeini L, Cooper T: Histamine excess symptoms in basophilic chronic granulocytic leukemia. Arch Int Med 131:560-562, 1973
16. Olinger EJ, McCarthy DM, Young RC, et al: Hyperhistaminemia and hyperchlorhydria in basophilic granulocytic leukemia. Gastroenterology 71:667-669, 1976

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Necrotic Arachnidism

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ARACHNIDISM IN NORTH AMERICA was first discussed in the medical literature of the United States in 1872.[1] It was not until 1957, however, that the first article discussing Loxosceles species of spiders as the probable cause of necrotizing bites in the United States was published.[2] Since then the number of presumed and proved cases of necrotic arachnidism has greatly increased. The cases reported have ranged from insignificant blebs,[3] through troublesome necrotic lesions, to serious necrosis complicated by hemolytic anemia, diffuse intravascular coagulation and death.[4-6]

Until about ten years ago necrotic arachnidism was thought to be a problem only in the midwestern United States, but then reports of similar lesions from southern and southwestern states began to appear.[7] The first case in Mississippi for example, was recorded in 1962, but by 1971 a total of 31 necrotic spider bites were reported there.[8] By 1966 necrotic arachnidism had occurred as far west as Los Angeles, as far north as Indiana and as far south as Baja California.[9] Dr. Findlay Russell of the University of Southern California, Department of Neurological Research, has recorded about ten cases of such bites in Southern California. With its increased incidence, knowledge of the natural history, physiology, diagnosis and treatment of this condition is becoming more important to physicians throughout the United States.

Report of a Case

A 23-year-old man awoke, after sleeping on the couch at his sister's house, with sudden pain in his right ankle. He tried to walk but fell be-

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